Remarks

No new matter has been added by these amendments. Applicants have amended the specification to provide a title that is more descriptive of the subject invention (*i.e.*, the title as amended in the allowed parent application), to place the specification and claims into proper format for U.S. practice, to correct minor typographical errors in the specification (which were also corrected during prosecution of the parent case), to recite the sequence identification numbers next to the sequences in the text, and to direct the entry of the sequence listing into the appropriate location in the specification. Support for the foregoing amendments to the claims may be found throughout the specification as originally filed, and new claims 19-37 correspond substantially to claims 4 and 6-8 as originally filed in the application, and to claims 21, 22 and 27-39 which were added by preliminary amendment to the parent application prior to examination of that application on the merits. Hence, these amendments do not add new matter, and their entry and consideration are respectfully requested. Upon entry of the foregoing amendments, claims 1 and 21-39 are pending, with claims 1, 21, 27, 30, 32, 33, 34, 35 and 39 being the independent claims.

In accordance with 37 C.F.R. § 1.821, the paper copy of the Sequence Listing and the computer readable copy of the Sequence Listing submitted herewith in the above application contain no new matter and are the same.

It is respectfully believed that this application is now in condition for examination. Early notice to this effect is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

In the Title:

The title of the application as filed is deleted and replaced by the following new title:

-- Modulating the Permeability of a Physiological Barrier With an Agent that Modulates Tyrosine Phosphorylation --.

In the Specification:

In the specification at page 1, after the title, the following section is added:

-- CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of, and claims priority under 35 U.S.C. § 120 to, U.S. Appl. No. 08/648,182, filed December 23, 1997, which is a 371 of PCT/GB94/02543, filed November 18, 1994, the entire contents of which applications are incorporated herein by reference. --;

after the Cross Reference section and before the first line of the text (*i.e.*, before line 3), the following section and subsection headers are inserted:

-- BACKGROUND OF THE INVENTION

Field of the Invention --;

and at line 5, before the text of the second full paragraph on page 1, the following subsection header is inserted:

-- Related Art --.

In the specification at page 5, line 7 (*i.e.*, prior to the beginning of the first full paragraph of text on page 5), the following section header is inserted:

-- BRIEF SUMMARY OF THE INVENTION --.

In the specification at page 6, line 28 (*i.e.*, prior to the beginning of the paragraph appearing at lines 29-32), the following section header is inserted:

-- BRIEF DESCRIPTION OF THE DRAWINGS --.

In the specification at page 9, line 26, after "p100" the following is inserted: -- (SEQ ID NOs: 1-5) --;

at line 27, after "p120" the following is inserted -- (SEQ ID NOs: 1, 6-9) --; and

after line 30 (*i.e.*, prior to the paragraph beginning at line 32 and bridging pages 9 and 10), the following section header is inserted:

-- DETAILED DESCRIPTION OF THE INVENTION --.

In the specification at page 15, line 21, please delete "associates" and substitute therefor -- associated --.

In the specification at page 17, line 14, after "achieved" please insert -- , -- (a comma); and after "either" please delete the comma and insert therefor -- directly or --.

In the specification at page 33, line 19 (*i.e.*, before the paragraph appearing at lines 20-22), the following subsection header is inserted: -- EXAMPLES --.

In the specification at page 58, line 7, after "sequenced" please insert -- (SEQ ID NOs: 1-9); and at line 8, after "p120" please insert -- (see Fig. 19) --.

After page 71 and before the drawings, the Abstract appended hereto as page 72 is inserted.

After the drawings, the sequence listing appended hereto (pages 1-4) is inserted.

In the Claims:

Claims 2-20 are sought to be canceled without prejudice or disclaimer.

New claims 21-39 are sought to be entered.

Modulating the Permeability of a Physiological Barrier With an Agent that Modulates Tyrosine Phosphorylation

CROSS REFERENCE TO RELATED APPLICATIONS

The present application is a continuation of, and claims priority under 35 U.S.C. § 120 to, U.S. Appl. No. 08/648,182, filed December 23, 1997, which is a 371 of PCT/GB94/02543, filed November 18, 1994, the entire contents of which applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to the control of permeability of the blood-brain barrier and other physiological barriers.

Related Art

The blood-brain barrier serves to separate the molecular, ionic and cellular environment of the blood from that of the brain. To a major degree, this separation is achieved by inter-endothelial tight junctions of high electrical resistance which greatly diminish paracellular flux. It is clear that the permeability of the tight junctions of the blood-brain barrier is not immutable. Rather, permeability appears to undergo dynamic regulation, especially by second messenger pathways.

Acquiring the ability to manipulate the permeability of the tight junctions of the blood-brain barrier is important for a number of reasons, among which are the following:

(i) To decrease brain oedema following stroke by closing the tight junctions of the blood-brain barrier;

(ii) To deliver blood-borne, membrane-impermeant drugs to the brain by reversibly opening the tight junctions of the blood-brain barrier; and

(iii) To block the entry into the brain of both leukocytes that mediate an immune response, such as occurs in multiple sclerosis, and metastatic cancer cells that may form tumours. (It is believed that during cell trafficking across the endothelium, the migrating cell passes through the tight junction

Modulating the Permeability of a Physiological Barrier With an Agent that Modulates Tyrosine Phosphorylation

ABSTRACT

Permeability of the blood-brain barrier and other physiological barriers can be modulated by the degree of tyrosine phosphorylation of proteins. Agents which promote tyrosine protein dephosphorylation reduce the permeability of the blood-brain barrier and those which promote phosphorylation increase permeability. Increasing blood-brain barrier permeability is useful in delivering drugs having a desired effect upon the central nervous system; decreasing blood-brain barrier permeability and other physiological barrier permeability is useful in preventing undesired compounds reaching the CNS and in certain clinical conditions.